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Association of serum alpha-fetoprotein (AFP) with indirect prognosis in gastric cancer

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ABSTRACT

Aims: Alpha-fetoprotein (AFP) is a glycoprotein secreted from the yolk sac and hepatocytes during fetal life. Elevated levels in adults are considered markers for yolk sac tumors, hepatocellular carcinoma and gastric cancer. There is still no consensus on the definition of AFP-secreting gastric cancers, but AFP-secreting gastric cancers have been reported to have a worse prognosis. In this study, AFP levels in gastric cancers with high AFP were compared with pathology results and evaluated in terms of indirect prognosis.

Methods: Patients with gastric cancer operated in the General Surgery Clinic of Ankara Bilkent City Hospital between 2019 and 2023 were retrospectively screened. Among the screened patients, those whose information could not be reached and those with incomplete information were excluded and 126 patients were included in the study. Serum AFP levels of these patients were compared with pathology results, stages and tumor sizes.

Results: The mean age of the patients in our study was 66±11 years, 42 (33.6%) were female and 84 (66.7%) were male. Of the 126 patients analyzed in the study, 107 (84.9%) were AFP-negative and 19 (15.1%) were AFP-positive. There was no significant difference in AFP levels between all patients in terms of liver metastasis, peritoneal metastasis, disease stage, perineural invasion and tumor location. However, serum AFP levels were significantly higher in patients with lymphovascular invasion and lung metastases (p=0.042; p=0.024). In the analysis for serum AFP level in the presence of lymphovascular invasion, ROC value was 2.35 ng/ml, sensitivity 58.2%, specificity 55.9%, area under the curve (AUC) 0.618, 95% confidence interval (95% CI) 0.512-0.723 and p=0.028.

Conclusion: Lymphovascular invasion is a poor prognostic factor in gastric cancer. In this study, a significant correlation was found between serum AFP value and lymphovascular invasion. In gastric cancers without AFP secretion, a serum AFP value above 2.35 ng/ml may be indirectly associated with poor prognosis because it predicts lymphovascular invasion.

Keywords: Gastric cancer, alpha-fetoprotetin, lymphovascular invasion

INTRODUCTION

According to Globacan 2022 data, gastric cancer is both the fifth most common cancer in the world and the fifth most common cause of cancer-related deaths globally.[1] Although gastric cancer can be diagnosed earlier than in the past, the five-year survival rate is 36% for all stages, while this rate is considerably lower for advanced, poorly differentiated and signet ring cell type cancers.[2] Alpha feto-protein (AFP) producing gastric cancer is also associated with poor differentiation, metastasis and poor prognosis.[3]

AFP is secreted from the yolk sac, hepatocytes and some gastrointestinal cells during fetal life. Its secretion in the adult is considered pathologic and is considered a biomarker for yolk sac tumors of gonadal origin, hepatocellular carcinoma and some types of gastric cancer.[4] AFP-producing gastric cancers account for 1.5-15% of all gastric cancers.[5] AFP-producing gastric cancer has been reported to have more liver metastases and lymphovascular invasion than other gastric cancers.[5,6]

Lymphovascular invasion is known to be an independent prognostic factor in malignancies. Lymphovascular invasion means tumoral involvement of microvessels or tumor emboli in the endothelium. This is predictive for lymph node

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metastasis and distant organ metastasis.[7] Therefore, adjuvant chemotherapy is recommended for gastric tumors without lymph node metastasis but with lymphovascular invasion due to poor prognosis.[8]

In this study, we aimed to evaluate the predictive value of AFP for lymph node and distant organ metastasis and to compare it with postoperative pathology results based on the knowledge that serum AFP level is an indicator of poor prognosis in patients with gastric cancer.

METHODS

The study was initiated upon receiving approval from the Ankara Bilkent City Hospital Ethics Committee (Date: 22.05.2024, Decision No: TABED1-24-266). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

For the study, 243 patients who underwent surgery for gastric cancer (GC) in the General Surgery Clinic of Ankara Bilkent City Hospital between July 2019 and October 2023 were retrospectively reviewed.

Patients with GC who were under 18 years of age, pregnant women, patients with diseases that may cause high levels of AFP such as chronic liver diseases, cirrhosis, yolk sac tumor, teratoma and hepatocellular carcinoma and whose electronic records could not be accessed, perforation, cases requiring emergency surgery due to bleeding or volvulus (n=18), cases requiring surgery due to pyloric stenosis (n=4), cases with a diagnosis other than gastric adenocarcinoma (neuroendocrine tumor, lymphoma, gastrointestinal stromal tumor) (n=22) were not included in the study.

Demographic (age, gender), laboratory (carcinoembryonic antigen (CEA), Ca 19-9, AFP) and clinicopathological (tumor localization, distant organ metastasis and lymph node metastasis) data were analyzed from the medical records of the remaining 199 patients. Preoperative imaging modalities for staging computed tomography (CT), F18-fluorodeoxyglucose positron emission tomography/computed tomography (PET/CT) and distant organ metastases including liver, lung and peritoneal metastases were determined by reviewing intraoperative operative notes. Pathologic TNM staging (pTNM-AJCC cancer staging manual 8th gastric cancer) was performed from postoperative pathology specimens. Preoperative laboratory parameters of the patients were analyzed and patients with inaccessible CEA, Ca19-9 and AFP levels and patients who could not be clinically evaluated for distant organ metastasis by imaging methods were excluded from the study (n=73) (Figure 1). Serum AFP levels were measured with the ADVIA centaur XPT immuoassay system.

Statistical Analysis

All statistical tests were performed using IBM statistical package for the social sciences (IBM SPSS Corp.; Armonk, NY, USA), version 22 software. Kolmogorov Smirnov and Shapiro-Wilk tests were used to assess the normality of data distribution. Mean±standard deviation (SD) was shown for continuous variables. Differences in continuous variables were analyzed using Mann-Whitney U test or Kruskal-Wallis test. p value <0.05 was considered statistically significant.

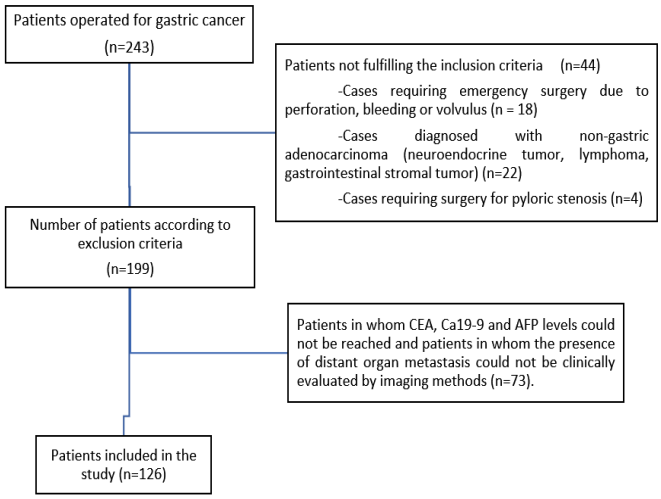
Patients operated for gastric cancer
(n=243)
Patients not fulfilling the inclusion criteria (n=44)
-Cases requiring emergency surgery due to perforation, bleeding or volvulus (n = 18)
-Cases diagnosed with non-gastric adenocarcinoma (neuroendocrine tumor, lymphoma, gastrointestinal stromal tumor) (n=22)
-Cases requiring surgery for pyloric stenosis (n=4)
Number of patients according to exclusion criteria
(n=199)
Patients in whom CEA, Ca19-9 and AFP levels could not be reached and patients in whom the presence of distant organ metastasis could not be clinically evaluated by imaging methods (n=73).
Patients included in the study (n=126)

Figure 1. Flowchart of patients included in the study

RESULTS

The mean age of the 126 patients included in the study was 66±11 years, 42 (33.6%) were female and 84 (66.7%) were male, 107 (84.9%) were AFP-negative and 19 (15.1%) were AFP-positive. The clinico-pathologic data of the patients are shown in Table 1.

The median, minimum, and maximum serum AFP levels were 2.6 ng/ml, 1.3 ng/ml and 14.0 ng/ml, respectively. Although there was no significant difference in AFP levels among all patients in terms of liver metastasis, peritoneal metastasis, disease stage, perineural invasion and tumor location, serum AFP levels were significantly higher in patients with lymphovascular invasion and lung metastasis, respectively (p=0.042; p=0.024).

In receiver operating characteristic (ROC) analysis for patients with lymphovascular invasion and lung metastasis, the cut-off values were 2.35 ng/ml and 4.15 ng/ml, respectively. In the analysis performed for serum AFP value in the presence of lung metastasis, sensitivity was 66.7%, specificity 80.5%, area under the curve (AUC) 0.879, 95% confidence interval (95% CI) 0.780-0.979 and p=0.000 (Figure 2, Table 2). In the analysis for serum AFP value in the presence of lymphovascular invasion, sensitivity was 58.2%, specificity was 55.9%, area under the curve (AUC) was 0.618, 95% confidence interval (95% CI) was 0.512-0.723 and p=0.028 (Figure 3, Table 2).

DISCUSSION

In the adult patient, elevated serum AFP primarily suggests hepatocellular carcinoma, other liver diseases and yolk sac tumors of gonadal origin. AFP-secreting gastric cancers have also been described and reported to be a poor prognostic criterion. In this study, we analyzed the serum AFP levels in gastric cancers and found that AFP levels were significantly higher in patients with lung metastases and in patients with lymphovascular invasion.

Lymphovascular invasion is one of the poor prognosis criteria in gastric cancers and it is known that this patient group should be evaluated for adjuvant chemotherapy.[9] Even in early-stage gastric cancers, adjuvant chemotherapy is recommended especially in T2 tumors even in the absence of

Table 1. Demographic data of the patients

	n (%)	Median (min-max)*	p value
Age	126	66±11	
Gender			
Male	84 (66.7)		
Female	42 (33.3)		
Liver			
No	119 (94.6)	2.5 (1.3-938.2)	0.353#
Yes	7 (5.6)	2.7 (1.3-80.6)	
Lung			
No	123 (97.6)	2.5 (1.3-938.2)	0.024#
Yes	3 (2.4)	4.9 (4.0-80.6)	
Peritoneum			
No	123 (97.6)	2.5 (1.3-938.2)	0.693#
Yes	3 (2.4)	3.9 (1.3-4.3)	
Stage			
I-II	49 (38.9)	2.5 (1.3-20.3)	0.542^
III	67 (53.2)	2.5 (1.3-938.2)	
IV	10 (7.9)	3.3 (1.3-80.6)	
Lymph node invasion			
No	36 (28.6)	2.3 (1.3-6.6)	0.060#
Yes	90 (71.4)	2.8 (1.3-938.2)	
Lymphovascular invasion			
No	34 (27.2)	2.3 (1.3-15.1)	0.042#
Yes	91 (72.8)	2.8 (1.3-938.2)	
Perineural invasion			
No	36 (29.3)	2.4 (1.3-20.3)	0.234#
Yes	87 (70.7)	2.7 (1.3-938.2)	
Location of the tumor			
Antrum	39 (31.0)	2.5 (1.3-80.6)	0.262^
Prepiloric	16 (12.7)	2.4 (1.3-15.1)	
Corpus	40 (31.7)	2.6 (1.3-938.2)	
Cardia	14 (11.1)	2.4 (1.3-6.9)	
EGJ	16 (12.7)	3.9 (1.3-177.5)	
Fundus	1 (0.8)	2.3 (2.3-2.3)	
Tumor size (cm)	126	5.6 (0.4-14.0)	
Serum AFP	126	2.6 (1.3-938.2)	

Abbreviations: *(Mean±Standart deviation), ^Kruskal-Wallis Test, #Mann-Whitney U test, Min: Minimum, Max: Maximum, EGJ: Esophagogastric junction, AFP: Alpha feto-protein

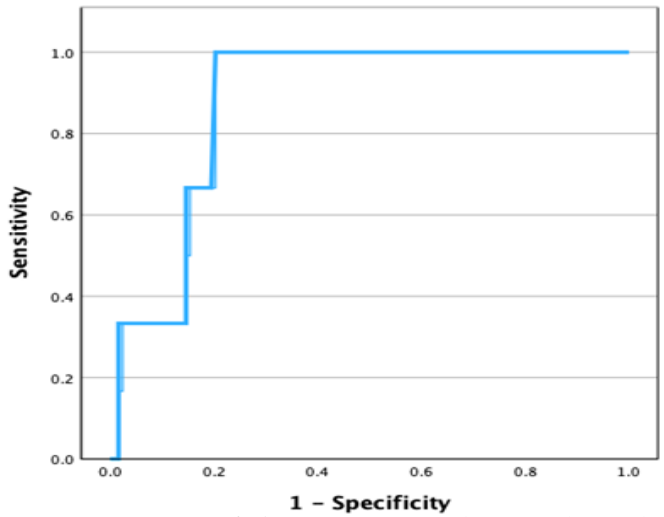

Figure 2. AFP ROC curve for lung metastasis [0.879 (0.780-0.979); p: 0.00)]

AFP: Alpha feto-protein, ROC: Receiver operating characteristic

Table 2. Cut-off for lung metastasis and lymphovascular invasion

Risk factor	AUC (95% CI)	Cutt-uf value	p	Sensitivity	Specifity
Lung metastasis	0.879 (0.780-0.979)	4.15	.000	66.7	80.5
Lymphovascular invasion	0.618 (0.512-0.723)	2.35	.028	58.2	55.9

AUC: Area under the curve

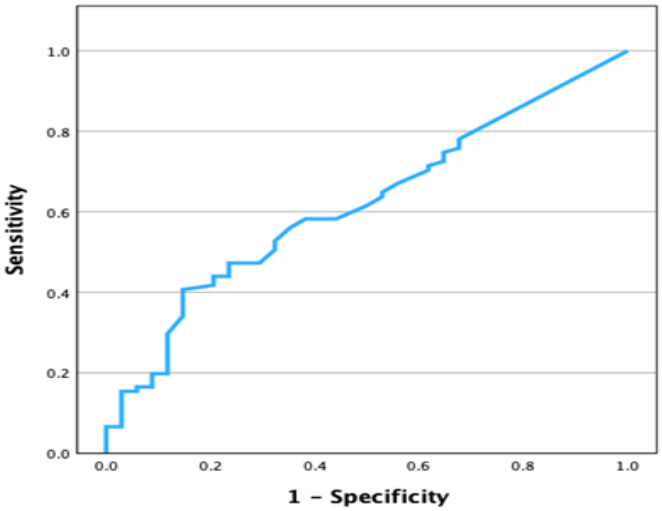

Figure 3. ROC slope for lymphovascular invasion [0.618 (0.512-0.723); p:0.028)]

ROC: Receiver operating characteristic

lymph node positivity.[10] Fujikawa et al.[7] reported pathological T, N and lymphovascular invasion as the most important prognostic indicators in gastric cancers. Lymphovascular invasion is an important risk factor for lymph node metastasis.[11,12] In early-stage gastric cancers, endoscopic mucosal-submucosal dissection can cure the disease. Although the presence of lymphovascular invasion in the pathology of the patient after endoscopic resection does not lead to resective surgery alone, it leads to resective surgery and lymph node dissection when criteria such as border positivity and tumor larger than 3 cm are added.[13] Although lymphovascular invasion is an important prognostic factor, it is a pathological data and there is no clinical and laboratory parameter to predict it. However, the significant correlation of AFP with lymphovascular invasion in this study may provide information about the presence of lymphovascular invasion in patients who have not yet undergone surgery.

Although the pathophysiology of AFP elevation in gastric cancer has not been clearly explained, clinically, the prognosis of this group of patients is poor. It is also speculated that AFP is elevated because gastric cancer metastasis pushes hepatocytes into regeneration and progression, and it is known that 33-72% of AFP-secreting gastric cancers present with liver metastases.[14] Although these types of tumors are prone to metastasize to the liver, liver metastases of other histologic types of gastric cancer and liver metastases of other organs do not raise AFP. In another study, it was reported that AFP is secreted from the yolk sac, hepatocytes and some gastrointestinal system cells in fetal life and its elevation in adults would be due to tumors of these regions.[4] However, the range of normal values of AFP in various publications and the values to define AFP-secreting gastric cancer vary.6 Chun and Kwon[15] set the threshold value as 7 ng/ml, Lin et al.[16] set it as 20ng/ml and Wang et al.[17] set it as 500 ng/ml. Therefore, there is no consensus for the definitive value. Since

the normal range of serum AFP value was determined as 0-8 ng/ml in the center where this study was performed, gastric cancer producing AFP above 8 ng/ml was defined as gastric cancer, but its direct relationship with liver metastasis could not be shown statistically. There was no difference in AFP values between patients with and without liver metastases, but there was a statistically significant difference between AFP values of patients with lung metastases and those without. Although the fact that only three patients had lung metastasis in this study reduces the statistical significance of AFP, it may give an idea about the prediction of lung metastasis in gastric cancers in daily practice.

The most important limitation of the study is its retrospective nature which may lead to missing records and documents. In addition, the limited number of patients, especially only three patients with lung metastases, is another limitation.

CONCLUSION

In gastric cancers, elevated AFP gives an idea about the presence of lung metastasis and lymphovascular invasion. Especially before endoscopic treatment in early-stage gastric cancer, serum AFP levels may predict lymphovascular invasion and guide the clinician to formulate an appropriate treatment plan.

ETHICAL DECLARATIONS

Ethics Committee Approval

The study was carried out with the permission of Ethical Committee of the Ankara Bilkent City Hospital (Date: 22.05.2024, Decision No: TABED1-24-266).

Informed Consent

Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Financial Disclosure

The authors declared that this study has received no financial support.

Author Contributions

All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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